Remarks

Applicant presents herewith facts and explanations showing that the written description rejection of the claims 44-57, 60-63 and 68-69 and the anticipation rejection of claims 58-59 and 64-67 with the April 30, 2010 dated Office action are mistaken. In addition, Applicant files herewith new claims 72-93 that are shown to comply with the 35 U.S.C. § 112, 1st paragraph and 35 U.S.C. § 102 even when the argumentation put forward for the April 30, 2010 dated rejections are viewed, for a moment, not mistaken.

I. Claim Rejections – 35 U.S.C. § 112 - 1st Paragraph

The Examiner stated that the doses to induce apoptosis of tumor cells to cause decrease of size or disappearance of a tumor recited in the instant claims 44-57, 60-63 and 68-69 are not well known in the art as shown by the prior art disclosures that treatments with cyclopamine and other inhibitors of Hedgehog signaling inhibited differentiation and did not induce apoptosis of tumor cells. The Examiner concluded that "Given this fact, it is not merely a matter of routine optimization to determine doses of Hedgehog signaling inhibitors that result in the claimed biological effects against tumor cells". The rejections are traversed.

Applicant points out that the presently claimed effects on tumor cells and tumors were unknown in prior art. However, the specification of the application clearly describes the claimed effects. Exemplifications of induction of apoptosis of tumor cells by use of a selective inhibitor of Hedgehog/Smoothened (Hh/Smo) signaling to achieve decrease of size or disappearance of tumors in human subjects while sparing their normal cells are also presented. The actual treatment results show that the treatment was effective each time it was applied and produced the claimed effects with more than seven separate tumors. Once informed about causation of a particular effect by administration of a given medicament, a person of ordinary skill in the art can readily adjust the dose for a patient to achieve the described effect.

A person skilled in the art routinely optimizes the doses of prior art medicaments for a particular patient to achieve previously known effects. This is the standard medical practice. Furthermore, the specification describes an advantageous beneficial / adverse effects ratio unprecedented in the art over a broad dosage interval making dose optimization particularly easy in case of present treatment. The skilled person is well versed in optimizing doses of prior art medicaments to achieve a known effect even when there is a small difference between a therapeutic and lethal dose. See the examples of prior art cancer chemotherapy presented with the January 21, 2010 response in this application.

Determining adequacy of written description compliance with 35 U.S.C.§112, first paragraph, requires an objective inquiry into the specification from the perspective of a person of ordinary skill in the art. Objective evaluation of the adequacy of disclosure include consideration of the existing knowledge in the field, extent and content of the prior art, the maturity of the science or technology in the field and predictability of the aspect at issue. In case of adjusting the dose of a medicament for a patient to achieve a previously known effect, the prior art knowledge was vast. This is the routine practice.

Finding out induction of apoptosis of tumor cells in a patient following treatment and making appropriate dose adjustments to achieve apoptotic elimination of tumor cells were well known in prior art. Concerning determination of morphological signs of apoptosis of tumor cells in tissue sections described in the exemplifications of invention, see e.g. van de Schepop HAM et al, *Journal of Clinical Pathology: Molecular Pathology* 1996;49:M214-M217 stating "*Apoptotic cells can be counted readily in haematoxylin and eosin stained tissue sections ... permit ... monitoring of the effects of treatment*".

Obtaining biopsies from patients before and during treatment and using various imaging modalities to monitor response to a given drug administration were also common knowledge and practice. See e.g. Symmans WF et al, *Clinical Cancer Research* 2000;6:4610-4617 reporting "*FNA is a quick minimally invasive procedure ... Serial fine-needle aspirations were obtained before treatment and at 24, 48, 72 and 96 h after first paclitaxel dose. Microscopic counts of apoptotic indices were performed. The change in cancer volume from treatment was determined* *using radiological measurements ... apoptotic response for the first 4 days inversely correlated with ... residual cancer ... more frequent ... dosing might be beneficial ... Early prediction of the likely response to treatment could facilitate early modifications to improve an individual's neoadjuvant therapy*". Noninvazive methods to determine induction of apoptosis of tumor cells in vivo in response to a medicament administration were also known in prior art (see e.g. Hakumaki JM et al, *Cancer Research* 1998;58:3791-3799).

Thus, a person of ordinary skill in the art presented with the specification of application could readily and objectively monitor the response to administration of an instant medicament to a tumor patient and optimize the dose to achieve decrease of size or disappearance of a tumor by inducing apoptosis of tumor cells. Besides finding out from the exemplifications of invention with actual treatments of > 7 human tumors, the skilled person clearly understands from further written description and explicit teachings that the Applicant was in possession of the doses causing the recited effects. See

page 11, lines 22-27 "*preservation of the undifferentiated cells ... provides information about tolerable doses in other possible modes of administration ... e.g. ... systemic*",

page 15, lines 19-24 "*Causation of the highly efficient differentiation and apoptosis of the tumor cells ... at doses that preserve the undifferentiated tissue cells ... support the use ... on ... internal tumors*",

page 19, lines 6-29 "*Effectiveness on several independent tumors in unrelated patients with differing genotypes is consistent with the general utility*",

page 23, lines 18-27 "*... normal tissue cells are preserved ... but said administration suffices for ... apoptosis of said tumor cells*".

The original application therefore clearly conveys to a person skilled in the art that the Applicant was in possession of the doses to produce the claimed effects.

Appendix A filed herewith shows confirmations by independent post-published investigations that the tumor treatment described in the present application can provide decrease of size or disappearance of cutaneous and internal tumors by inducing apoptosis of tumor cells while sparing normal cells. Genetic methods of downregulating or eliminating a protein essential for a particular signaling provide ultimate selective means of inhibition of that signaling in an animal. They can also provide conditional inhibition for various durations. Hutchin ME et al, *Genes & Development* 2005;19:214-223 for example reported investigations employing such genetic methodology. Their results confirm that the present tumor treatment is indeed generic and can provide apoptotic elimination of tumor cells while sparing normal cells. Basic biological reasons also exist for the unprecedented therapeutic efficacy of the originally described tumor treatment every time it has been applied; it is a rational intervention designed to take advantage of an essential difference between the normal cells and tumor cells having stem cell features (see Tas S, *Melanoma Research* 2006;16:S99 and Tas S, *A Fundamental Vulnerability Of Tumor Cells* filed with the June 11, 2007 Amendment). Post-published investigations clearly verified that any pharmaceutically acceptable selective inhibitor of Hh/Smo signaling can be used to induce apoptosis of tumor cells to cause decrease of size or disappearance of tumors independent of their histopathological classification and that this achievement requires administration of a dose beyond that suffices to inhibit proliferation of tumor cells (see Appendix A). Nothing different than described in the originally filed specification is described in these post-published confirmations for said achievement. Various routes of drug administration that are commonly employed in the art (including oral and other systemic) have been shown to be suitable. Thus, a person of ordinary skill in the art presented with the originally filed specification readily and reproducibly achieves the therapeutic effects recited in the claims independent of the histopathological class of tumor and by any route of drug administration appropriate for the localization of tumor.

It should finally be pointed out that medical practice does not rely on tables where mg/kg/day values are shown for each route of administration, patient age, body mass index and other parameters known to influence the optimal dose. A skilled person knows well that the optimal dose of a medicament for a patient may change even from one day to the other, e.g. due to changes in the renal or hepatic functions of the patient and he or she is well versed in dose optimization once informed about the therapeutic effect to be produced. The dose of a particular drug to be administered to a patient is routinely adjusted so as to produce a known or expected effect. Adjusting the dose of a medicament is clearly not a "hit-or-miss" but a routine in the art.

At least for the aforementioned reasons and for others given previously, the specification has adequate written description that conveys to a skilled person that the Applicant was in possession of the doses to produce the claimed effects.

II. Claim Rejections – 35 U.S.C. § 102(e)

Claims 58-59 and 64-67 have been rejected under 35 U.S.C. § 102 (e) as being anticipated by Dudek et al (USP No. 6,291,516) stating that both Dudek et al and instant claims describe medicaments comprising cyclopamine or another Hedgehog antagonist. Examiner did not view the instructions recited in the claims 58-59 and 64-67 to have patentable weight stating that "If the Examiner were to accept Applicants' arguments, inventors could repeatedly patent the same medicament by merely changing the instructions provided therewith". The rejections are traversed.

The argumentation put forward for the rejections of claims 58-59 and 64-67 is unfounded for multiple reasons.

First, it is untrue that a previously known pharmaceutical composition could be repeatedly patented by merely changing the instructions provided therewith when the instructions fail to describe a novel and unobvious use. A previously known composition combined with instructions that provide a novel and unobvious use is what is being sought to be patented here. A prescription drug is a particular product where instructions describing its uses are required by law. Since a prescription drug is administered to a patient to produce a known or expected effect, a prescription drug's container or package necessarily contains instructions for a process and the law demands such instructions as an integral part of a pharmaceutical product. A medicament claim can thus entail recitation of both a compound and a process of using it to obtain a particular therapeutic effect.

It has long been held that a programmed general purpose computer creates a new machine. See *In re Alappat*, 31 USPQ2D 1545, 1558 (Fed. Cir. 1994). The rationale is that the computer is capable of new functions by reason of the new instructions.

Instructions for use are required for all medicament packaging as a matter of Federal law and commonly include dosing to a specified observable result. Such information is essential to the practical capability of a medicament to affect a therapeutic result. The instructions here provide the medicament with an additional functionality directly analogous to that instructions programmed into a general purpose computer. The presence of novel and un-obvious instructions therefore does provide a real basis for patentability of a medicament.

In the present case, it is clear that without instructions such as recited in the claims 58-59 and 64-67, and also in new claims 82 and 83, a skilled person would not obtain the desirable novel effects and therapeutic results recited in the claims. It is further self-evident that the instructions recited in the claims must be used with a recited medicament to obtain decrease of size or disappearance of a tumor by eliminating the tumor cells by apoptosis. Hence, a functional relationship clearly exists between the printed matter and substrate. The claims 58-59 and 64-67 thus describe subject matter patentable under US law.

Applicant would also like to point out for the record that a medicament having instructions for inhibition of tumor cell proliferation and comprising cyclopamine or another Hedgehog antagonist would not have been patentable to Dudek etal. The reason is not that the instructions could be ignored in the analysis, but rather because use according to the instructions was already known. Inhibition of Hedgehog signaling by cyclopamine as well as the use of a selective inhibitor of Hedgehog signaling for inhibition of tumor cell proliferation were publicly known prior to the earliest priority claimed in Dudek et al (see e.g. Coventry S et al, *Pediatric and Developmental Pathology* 1998;1:29-41 and Fujita E et al, *Biochemical and Biophysical Research Communications* 1997;238:658-664).

Other facts, presented with the January 21, 2010 response and with the earlier amendments in this application, also show that the presently claimed invention is novel and patentable over Dudek et al and over entire prior art for further reasons as well. The effects and therapeutic results recited in the instant claims are not inherently present in a prior art use known for cyclopamine or for another selective inhibitor of Hh/Smo signaling. Reference is made to said response and amendments to avoid unnecessary repetition.

III. New Claims

New claims 72-81 and 84-93 recite methods for tumor treatment. The method claims 72, 74-79, 80-81 and 92 recite a step of observing induction of apoptosis of the tumor cells. Claims 74, 75 and 81 are limited additionally by reciting that the apoptotic elimination of tumor cells is caused while sparing the normal cells having stem cell features. New claims 82-83 recite medicaments and explicitly refer to labeling that provides instructions to obtain the recited therapeutic effects in a tumor-bearing human. Claim 83 is limited additionally by reciting the described sparing of the normal cells of patient. New claims 84-89 depend on any of claims 72-76 or 79-83 and recite further limitations from the specification of application.

Assays to determine apoptosis were common knowledge and routinely used in prior art. The specification of the application describes use of one of these that is particularly suited in the routine pathology practice (van de Schepop HAM et al, *Journal of Clinical Pathology: Molecular Pathology* 1996;49:M214-M217; see Willingham MC, *The Journal of Histochemistry and Cytochemistry* 1999;47:1101-1109 for the various assays used in prior art). A person of ordinary skill in the art presented with the specification of application would readily perform the recited observation of induction of apoptosis of the tumor cells to adjust the dose for a patient. Likewise various imaging modalities to monitor size and location of tumors were routinely practiced in prior art. The skilled person could therefore readily monitor the effects of a medicament administration on a tumor and determine causation of decrease of size or disappearance of a tumor.

Regarding claims 74, 75, 80-81, 83, 93 support is specifically provided at, e.g. page 15, lines 4-17; page 19, lines 12-27 of the originally filed application. Immunohistochemical analyses employing an antibody that marks both tumor cells and the normal cells having stem cell features are described and the present treatment inducing differentiation and apoptosis of the tumor cells is described to spare said normal cells. The monoclonal antibody Ber-EP4 used in the exemplifications of present invention was well known in prior art to recognize the human epithelial cell adhesion molecule (EpCAM) expressed by the normal stem cells and multipotent progenitor cells besides most cancer cells. Various other anti-EpCAM monoclonal antibodies (including humanized antibodies for administration to human) and other methods of detecting EpCAM were widely used in prior art (see the scientific publications referenced in the Appendix A filed on March 18, 2009). Damaging of the normal stem cells and progenitor cells of tumor-bearing patients by the various prior art chemotherapy-radiotherapy protocols were known to severely limit their utility and the specification of application has description of an unprecedented selectivity of the present treatment sparing said normal cells. The skilled person presented with the specification would thus understand that preservation of said normal cells of a patient can be readily determined by employing an antibody that marks them.

Other facts showing novelty, unobviousness, written description and enablement of the subject matter recited in the new claims 72-93 have been presented with the January 21, 2010 dated reply and earlier amendments in this application.

IV. Conclusion

The claims have adequate written description complying with the 35 U.S.C. § 112, 1st paragraph and are novel over prior art. The claims recite subject matter patentable under US law. Early and favorable action thereon is requested.

Respectfully submitted,
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Appendix A (U.S. Patent Application No.: 10/682584)

Independent Confirmations That Carrying Out the Originally Described Tumor Treatment Provides Apoptotic Elimination Of Tumor Cells To Cause Decrease Of Size Or Disappearance Of Tumors Independent Of Histopathological Classification

Post-published investigations have independently confirmed that the teachings of the originally filed specification are operative and a selective inhibitor of Hedgehog/Smoothened (Hh/Smo) signaling can be used to eliminate tumor cells of a patient by inducing apoptosis independent of the histopathological classification of tumor. They verified further that despite an absolute dependence of normal stem cells on Hh/Smo signaling, a selective inhibitor of it can be administered until inducing apoptotic elimination of the tumor cells while sparing normal stem cells and progenitor cells that are commonly damaged by prior art nonsurgical tumor treatments. That achievement of decrease of size or disappearance of a tumor by induction of apoptosis of tumor cells requires administration of a selective inhibitor of Hh/Smo signaling in a dose beyond that suffices to cause complete inhibition of proliferation of the tumor cells has also been verified.

An animal comprises of a practically immeasurable number and variety of molecules and molecular interactions. Genetic engineering designed to inhibit or eliminate a signaling protein or an essential transducer of the signaling initiated by it provides an ultimate selective means of inhibition of a particular signaling to various degrees and for various durations. Hutchin ME et al, *Genes & Development* 2005;19:214-223 described that transgenic mice engineered to have sustained Hh/Smo signaling in the epidermis-hair follicle lineage cells consistently developed tumors of said lineage in an age-dependent manner. The gli2 transgene used for the activation of Hh/Smo signaling was engineered to be responsive to a compound that normally does not exist in the body of mice (doxycycline). Oral administration of doxycycline to tumor-bearing animals to inhibit expression of Gli2 from the transgene and to inhibit thereby the Hh/Smo signaling was continued for various durations. A dose-dependent inhibition of the gli2 transgene and of Hh/Smo signaling is described to be caused with doxycycline (page 215, right column, paragraph 2 to page 216; Figure 2). Since the endogenous gli2 gene is unaffected by doxycycline and the cells continued to be capable of responding to the Hh secreted by the Hh-synthesizing tissue cells, the animals engineered by Hutchin et al provided a means of returning the Hh/Smo signaling in the cells expressing the transgene to about normal levels without completely shutting down all signaling (see page 216, Figure 2I, Gli2 RT-PCR).

Hutchin et al describe that doxycycline administration to the tumor-bearing animals caused inhibition of

Hh/Smo signaling in tumor cells already on day 1 and the tumors showed markedly increased frequency of apoptosing tumor cells by day 3 to lead to decrease of tumor volume during the following days to result in about 90% decrease of tumor volume in 3 weeks (page 216, left column, page 217, Figure 3). The regressed tumors showed also signs and markers of differentiation of tumor cells (page 216, left column, last paragraph to page 217, right column, paragraph 1; Figure 4). Thus, the experimental results reported by Hutchin et al confirm that administration of a selective inhibitor of Hh/Smo signaling can be used to induce differentiation and apoptotic elimination of tumor cells.

Hutchin et al also describe that a doxycycline dose sufficing to make all tumor cells nonproliferative did not suffice to induce differentiation and apoptotic elimination of the same tumor cells. See page 216, right column, paragraph 1 (*"... all ... regressed tumors examined [100 %, n= 15] were nonproliferative by Ki67 immunofluorescence ... all regressed tumors retained expression of the follicle outer root sheath marker K17"*). See also Figure 4. Since K17 is a marker of the undifferentiated cells of the outer root sheath (where stem cells and multipotent progenitor cells reside), persistence of K17 expressing tumor cells following a treatment that caused all K17 expressing tumor cells nonproliferative (see Figure 4 d, e, f, g) confirms that inhibition of proliferation of tumor cells by use of a selective inhibitor of Hh/Smo signaling suffices neither for differentiation nor for apoptotic elimination of tumor cells.

In addition, occurrence of K1 expressing residual tumor cells in the regressed tumors (Figure 4h, i) shows that the amount of doxycycline reaching to them and sufficing to induce their differentiation did not suffice to induce their apoptotic elimination. Notice that in the tumor-bearing animals engineered by Hutchin et al, the tumor cells that happen to be near a Hh-secreting cell continues to have Hh/Smo signaling and those tumor cells away from a Hh source would cease Hh/Smo signaling upon exposure to a sufficient dose of doxycycline.

Hutchin et al do not report an adverse effect of the treatment on normal skin tissue of animals. They show rather results showing that the normal cells in the basal layer of epidermis, where the normal stem cells and progenitor cells are known to reside, were unharmed following a dose that caused about 90 % decrease of tumor volume (see e.g. Figure 4d).

The descriptions by Hutchin et al confirm those in the originally filed specification in this application that a dose of cyclopamine that consistently caused arrest or inhibition of proliferation of all residual BCC cells did not suffice for the apoptotic elimination of same tumor cells (page 6, lines 10-15; page 14, line 26 to page

15, line 2; see also the Appendix A filed with the March 18, 2009 dated Amendment in this application). Likewise, the specification describes that apoptotic elimination of tumor cells requires exposure of them to cyclopamine in a dose that is even greater than that suffices to induce differentiation of them (see the Appendix A filed on 03.18.2009).

Post-published investigation verified also that a selective inhibitor of Hh/Smo signaling (e.g. cyclopamine) can be used to cause apoptotic elimination of tumor cells of non-skin tumors as well when administered in a dose beyond that suffices to inhibit proliferation of the tumor cells. *Patched* haploinsufficiency, for example, is known to underlie the nevoid basal cell carcinoma syndrome and to lead to development of markedly increased frequencies of various tumors in an age-dependent manner both in skin and internally. Romer JT et al, *Cancer Cell* 2004;6:229-240 and Sanchez P et al, *Mechanisms of Development* 2005;122:223-230 described that *patched* haploinsufficient animals diagnosed to have brain tumors classified as medulloblastoma show upregulation of Hh/Smo signaling in tumor cells in comparison to normal cells and that their treatment with a selective inhibitor of Hh/Smo signaling provided apoptotic elimination of the tumor cells. Systemic administration of a selective inhibitor of Hh/Smo signaling in a dose inducing apoptosis of tumor cells to cause decrease of size or disappearance of brain tumors is reported to cause no deleterious effects in treated animals (Romer et al, *ibid*). That the achievement of induction of apoptosis of tumor cells requires administration of a dose of cyclopamine greater than that suffices to inhibit proliferation of the same tumor cells (medulloblastoma in this case) was also confirmed (Sanchez et al, *ibid*).